REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 1-18, 20-23, 26-28, 33, 37-46, and 49-51 are pending, and claims 1, 18, 37, 42 and 49 are independent. Claims 19, 24-25, 29-32, 34-36 and 47-48 are canceled, without prejudice to or disclaimer of the subject matter therein. Claims 1-17 and 23 are withdrawn as non-elected. With claims 49-51 added, claims 18, 20-22, 26-28, 33, 37-46, and 49-51 will be under consideration.

II. The Amendments to the Claims

Claims 18, 37 and 42 are revised to recite the step of deleting a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21. The claims are also amended to delete reference to human chromosome 14. Support for the amendments to claims 18, 37 and 42 may be found throughout the specification, including paragraph [0116] of the published version, US 2006/0185025.

Claims 21-23 are revised to provide proper antecedent basis. Support for this change is apparent, for example, from paragraphs [0074] and [0116]. *Id.*

New claim 49 is drawn to a method for producing a human artificial chromosome vector. There is support for this claim throughout the specification, including paragraphs at [0021]-[0022], [0026], [0074], and [0116].

New claim 50 specifies that the distal region within the 21q11 region of the long arm comprises AL163204 and the centromere side of the long arm of the human chromosome 21. New claim 51 specifies that the distal region within the 21p11 region of the short arm comprises AL163201 and the centromere side of the short arm of the human chromosome 21. Support for these

new claims may be found throughout the specification, including paragraph [0116] of the published version, US 2006/0185025.

Claim 20 is amended to correct claim dependency, and claims 21-23, 26-28, 33, 40 and 45 to delete multiple dependency.

These changes do not introduce any new matter, and so their entry is respectfully requested.

III. The Objection to the Specification

At page 4, the Office Action objects to the specification, asserting that hyperlinks are present there. The present amendment deletes hyperlinks for the specification, mooting the objection. Reconsideration and withdrawal of this ground of objection are requested, therefore.

IV. The Objection to the Claims

The Office Action also objects to claims 22, 26-28 and 33, alleging improper multiple dependency. In view of the claims revisions above, eliminating such multiple dependency, reconsideration and withdrawal are requested.

V. The Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 19 and 20 stand rejected for alleged indefiniteness in the phrases "high efficiency" (both claims) and "derived from" (claim 20). Without acquiescing to these stated grounds for rejection, applicant has chosen to advance prosecution by canceling claim 19 and amending claim 20 to delete both of these the phrases. Withdrawal of this ground of rejection is requested, therefore.

VI. The Rejection Under 35 U.S.C. § 112, First Paragraph

At pages 5-9, the Office Action advances a "non-enablement" rejection claims 41 and 46. In particular, the Office acknowledges that the specification is enabling for the production of mouse embryonic stem cells but not for producing embryonic stem cells for other organisms.

In traversing this ground of rejection, applicants would emphasize the observation in the M.P.E.P. at Section 2164.08, that:

> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without `undue experimentation'." *In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).* Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).* All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. *See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).*

With regard to claim breadth, moreover, Section 2164.08 states:

> As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971).*

With this understanding, applicants further note that claims 41 and 46 recite the use, pursuant to the inventive method, of a pluripotent cell used that is an embryonic stem cell (ES cell), a mesenchymal stem, cell or a tissue stem/precursor cell. At the time the present invention was made, embryonic stem cell lines from many sources were available, including mouse ES, human ES, rhesus monkeys ES, and rhesus ES. For example, see Thomson *et al.*, *Science* 282: 1145-47 (1998) (Exhibit A to this response).

Thus, a skilled person would have had full access to ES cells from a variety of organisms. Furthermore, applicants have amply described their invention in terms that enable the skilled person to implement the claimed methodology, in keeping with relevant M.P.E.P. guidelines. Thus, as to the transfer of foreign DNA from a HAC vector, as claimed, to recipient cells, the specification teaches that:

> The HAC vector or the HAC vector containing foreign DNA can be transferred from the cell retaining these vectors to other cells. The cells to which these vectors are transferred include, but not limited to, ***animal cells (mammalian cells)***. According to the present invention, preferably the Chinese hamster ovary (CHO) cell, which is known to allow for intact transfer of human chromosomes, is used. The CHO cell is known to form microcells efficiently, and the HAC vector can be further transferred from the CHO cell to other cells (cells other than the CHO cell). In addition, according to the present invention, ***the HAC vector can be transferred to pluripotent cells***. The term "pluripotent cell" means a cell capable of differentiation into particular cells or tissues through given procedures. Examples of pluripotent cells include cells that are capable, through procedures such as infusion into host embryos and formation of collective embryos, of differentiating into two or more types of cells or tissues in chimeric animals, such as ***embryonic stem cells (ES cells), embryonic germ cells (EG cells) and embryonic cancer cells (EC cells)***. Also included are cells capable of differentiating into bone cells, chondrocytes or adipose cells by culturing the cells in inducer medium supplemented with, for example growth factors (ex., transforming growth factor; TGF), more specifically somatic stem cells (ex., mesenchymal stem cells).
>
> ... The term "embryonic stem cell," or ES cell, as used herein refers to a cultured cell derived from an early phase embryo characterized by the ability to multiply while maintaining undifferentiated nature (totipotency). Embryonic stem cells are cell lines established by culturing the cells in the internal cell mass, which is undifferentiated stem cells present inside the blastocyst of the initial embryo of animals, so as to keep multiplying while maintaining an undifferentiated state. The term "embryonic germ cell," or EG cell, means a cultured cell derived from a primordial germ cell characterized by ability almost equivalent to that of the embryonic stem cell above.

Paragraphs [0148]and [0149] of US 2006/0185025 (quotations omitted, emphasis added).

Along these lines, Example 4 of application evidences that successful transfer a HAC vector, as presently recited, into chicken cell lines and human cell clones, respectively. Example 21 likewise demonstrates that HAC vector transfer into human stem cells.

Moreover, Example 14 documents mediation of EPO gene-transfer via a HAC vector, pursuant to the claimed invention, into normal human fibroblast cells, resulting in expression of EPO protein. Similarly, Example 19 describes how a GFP gene, inserted into the HAC vector derived from chromosome 21, was transferred successfully into human cell clones.

Finally, Example 22 demonstrates that mesenchymal stem cells, retaining such a HAC vector, kept their multi-potency to bone, cartilage, and adipose cells, respectively.

It is apparent, therefore, that the skilled person, informed by the original specification, can readily identify and produce an illustrative variety of embryonic stem cells that retain a HAC vector, pursuant to applicants' claimed invention. Accordingly, the enabling description in that specification is commensurate in scope with the present claims. Reconsideration and withdrawal of this ground of rejection are respectfully requested, therefore.

VII. The Rejections Under 35 U.S.C. § 103(a)

A. The Rejection of Claims 18-21, 26-27, 33 and 37-46

The Office Action rejects claims 18-21, 26-27, 33, and 37-46 over Kuroiwa *et al.*, *NAR* 26: 3447-48 (1998) ("Kuroiwa '98") in view of Kuroiwa *et al.*, *Nature Biotechnology* 18: 1086-90 (2000) ("Kuroiwa '00"), and Tomizuka *et al.*, *Nature Genetics* 16: 133-43 (1997) ("Tomizuka"). Applicants respectfully traverse this ground of rejection.

1. Summary of the claimed invention

Present claims 18, 37, and 42 recite a methodology comprising the deleting of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21.

2. The cited publications do not teach or suggest the telomere-side deletion(s) that are presently recited

Kuroiwa '98 teaches the transfer of human chromosome 22 into DT40 cells from mouse A9 cells. Kuroiwa '98 fails suggests nothing about a HAC vector in which a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21 have been deleted.

The cited secondary references fail to remedy the deficiencies of Kuroiwa '98. In fact, Kuroiwa '00 reports the cloning of a defined human chromosomal region into a stable minichromosome vector by telomere-directed chromosome truncation, and Tomizuka describes the transmission of a human chromosome fragment in chimaeric mice. Thus, these publications fail to teach or suggest the aforementioned distal region deletion(s), a point that the Office has acknowledged at page 14. For this reason alone, the rejection warrants reconsideration and withdrawal.

3. There would have been no reason for the skilled artisan to have combined the cited art in any manner implicating applicants' claimed invention

The Office contends that it would have been obvious to have substitute the human chromosome taught by the prior art with human chromosome 21, "because the simple substitution of one known element for another would have yielded predictable results" (Office Action at page 13).

Applicants must object to this characterization, since the prior art of record evinces no recognition that the category of human chromosomes would be fungible in this context, such that chromosome 21 and the disclosed chromosome were interchangeable. In any event, as demonstrated above, the skilled artisan would have gleaned nothing from the prior art any deletion of sequences required for a HAC vector as presently recited. For this reason, too, the obviousness rejection is improper and should withdrawn.

4. The claimed invention provides unexpected results that belie obviousness within the meaning of Section 103

A HAC vector, as recited, can be transferred to human normal fibroblasts and to human normal somatic cells other than fibroblasts. See, *e.g.*, paragraph [0151] of US 2006/0185025. Such a HAC vectors also is retained stably, for example, in chicken cell lines and human cell clones (Examples 4 and 18) and in human stem cells (Examples 21-22), *inter alia*.

These results are unexpected because, at the time the present invention was made, the prior art taught that human artificial chromosomes were ***not*** stable in mammalian cells. See Mills *et al.* *Human Molecular Genetics* 8: 743-53 (1999) (Exhibit B), in particular page 748, right column, through page 749, left column, and Table 1, and Heller *et al.*, *PNAS* 93: 7125-30 (1996) (Exhibit C), particularly Table 1. Accordingly, there was a clear prejudice in the art against the transfer of artificial chromosomes into mammalian cells, underscoring the surprising and, hence, patentable aspects of applicants' claimed invention.

For at least these reasons, the rejection of claims 18-21, 26-27, 33 and 37-46 under 35 U.S.C. § 103(a) is unsustainable. Its reconsideration and withdrawal therefore are requested.

B. The Rejection of Claims 22 and 28

The Office Action separately rejects claims 22 and 28 under Section 103(a), alleging unpatentability over Kuroiwa '98, Kuroiwa '00, and Tomizuka, *supra*, in view of Hattori *et al.* *Nature* 405: 311-19 (2000). Yet, while disclosing nucleotide sequences of the human chromosome 21 that achieve 99.7% coverage of 21q, Hattori suggests nothing about deleting a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21.

In relation to the present claims, therefore, the Office's allegation of obviousness do not validate an obviousness rejection. Reconsideration and withdrawal of the rejection is requested.

CONCLUSION

All of the stated grounds of objection and rejection have been traversed properly or rendered moot. Thus, the present application is in condition for allowance, and applicants request an early indication to this effect. Also, Examiner Hill is invited to contact the undersigned directly, should he feel that any issue needs further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is are required for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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